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EXPERIMENTAL STUDIES

Survival After Myocardial Infarction in Rats: Captopril Versus Losartan

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Objectives. **This study sought to compare the effects of angiotensin-converting enzyme inhibition versus angiotensin II receptor blockade on survival in rats with myocardial infarction.**

Background. **The effects of specific nonpeptide angiotensin receptor blocking agents on survival after myocardial infarction are unknown.**

Methods. **Rats with a moderate to large myocardial infarction were treated with captopril (2 g/liter drinking water, n = 87) or losartan (2 g/liter drinking water, n = 96). Therapy was initiated immediately after coronary artery ligation and continued for 1 year.**

Results. **Uncensored median survival in captopril-treated rats that survived at least 48 h was 201.5 days versus 236.0 days for losartan-treated rats (p = 0.066). Median survival censored for rats with lung infections was 201.5 days in captopril-treated rats versus 243.0 days for losartan-treated rats (p = 0.028). Conscious hemodynamic measurements and remodeling data obtained at 1 year in the surviving rats (n = 5 for captopril; n = 9 for losartan) revealed no differences in heart weight, left ventricular pressure, dP/dt, cardiac index, time constant of relaxation or any variable of left ventricular remodeling. The only differences (mean ± SD) were an increase in heart rate (293 ± 19 vs. 2[illegible] ± 15 beats/min, p < 0.05) and a decrease in peak developed pressure (153 ± 21 vs. 180 ± 16 mm Hg, p < 0.05) in the losartan-treated rats.**

Conclusions. **We conclude that in this experimental model of heart failure, there was no difference between survival after angiotensin II receptor blockade with losartan and with angiotensin-converting enzyme inhibition with captopril.**

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The use of angiotensin-converting enzyme inhibition is now established therapy for patients with chronic congestive heart failure (1–3) and for patients with systolic dysfunction after myocardial infarction (4,5). Angiotensin-converting enzyme inhibitors also appear to decrease the incidence of recurrent myocardial infarction, unstable angina and sudden death (2–4). Although these beneficial effects are well documented, the mechanism of action of these agents is not clear. It is generally believed that angiotensin-converting enzyme inhibitors exert their cardiac effects primarily by decreasing afterload and preload through inhibition of the conversion of angiotensin I to angiotensin II (6). The mechanisms of action of angiotensin-converting enzyme inhibitors may be more complex than simply afterload reduction, because laboratory (7) and clinical studies (2,8) show that a relatively pure afterload-reducing agent, hydralazine, is less beneficial than angiotensin-converting enzyme inhibitors. In the rat coronary artery ligation model of heart failure, captopril decreased left ventricular end-diastolic pressure, increased venous compliance and attenuated left ventricular dilation, whereas hydralazine had none of these effects (7). In addition, because serum angiotensin-converting enzyme inhibitor activity is not elevated during the chronic compensated phase of congestive heart failure, it is difficult to argue that blocking the effects of angiotensin-converting enzyme inhibitors would result in hemodynamic benefit (9). Thus, angiotensin-converting enzyme inhibitors may exert beneficial effects in addition to those predicted from the pharmacologic actions of these agents on the plasma renin-angiotensin system. Potential explanations for the mechanism of action of angiotensin-converting enzyme inhibitors are their effects on the kinin and prostaglandin systems (6,9–14).

Losartan is a nonpeptide angiotensin II receptor blocker that lacks bradykinin-potentiating effects. When the hemodynamic effects of losartan and captopril were compared in experimental heart failure, both agents decreased left ventricular end-diastolic pressure, decreased left ventricular end-diastolic volume and increased venous compliance without a change in heart rate (15). In addition, a recent report (16) showed that both enalapril and losartan equally attenuated the development of myocardial fibrosis in the noninfarcted rat left ventricle.

Because both captopril and losartan improved left ventric-

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ular hemodynamic variables in the rat model of heart failure after myocardial infarction, and captopril has been shown to improve long-term survival, the present study was designed to examine the effects of losartan on survival. The hypothesis was that there would be no difference in survival in rats treated with losartan or captopril after experimental myocardial infarction.

Methods

Coronary ligation model. Male Sprague-Dawley rats (175 to 275 g) underwent coronary artery ligation using techniques similar to those described previously (7,15). The study was performed in an AAAI AC-accredited facility with approval from the animal use committees of the Tucson Veterans Affairs Medical Center and the University of Arizona. After coronary ligation, rats were returned to their cages and randomly assigned to treatment with losartan (2 g/liter drinking water) or captopril (2 g/liter drinking water) using a balanced-block randomization process. Previous dose-ranging studies (15) showed that losartan shifts the log-pressure response curve to angiotensin II and that in these doses, losartan and captopril have similar hemodynamic effects in rats with heart failure. The rats were allowed access to their respective drinking water and standard rat chow ad libitum. Rats were housed in clear polyethylene cages not exceeding two rats per cage and were placed in individual cages when they grew to >500 g. Cages assigned to losartan and to captopril were placed alternately on the cage racks. All rats were housed in a single room of the animal facility with a 12-h light–dark cycle and independent ventilation, temperature and humidity control. Animals were weighed monthly and observed for 1 year.

Ten to 14 days after operation, rats were anesthetized with methoxyflurane, and a nine-lead electrocardiogram (ECG) with six limb leads and three chest leads was recorded. Only rats with ECG evidence of moderate to large myocardial infarctions on the basis of described criteria (7,15,17) were continued in the study.

Cages were inspected for dead animals daily. The date of death and the animal's weight were noted. A postmortem examination was performed, and the lungs were inspected for gross signs of consolidation. The lungs and heart were placed in formalin for subsequent necropsy studies.

Pathologic studies. The formalin-fixed lungs were dissected from the heart and examined for areas of consolidation. A scoring system for evidence of infection was applied to each specimen (18). Myocardial infarct size was measured in all animals using the endocardial circumference technique described previously (7,15). As in previous work, rats were considered to have a moderate to large infarction when ≥20% of the left ventricular surface area was occupied by fibrous scar tissue (18). Group stratification was confirmed at postmortem examination by quantitative left ventricular histopathologic studies.

Hemodynamic studies. Left ventricular function was evaluated in the surviving rats at the end of the trial. In brief, rats were anesthetized with methoxyflurane, and a 1-mm micromanometer-tipped catheter (Millar Instruments) was inserted into the right carotid artery. The catheter was advanced into the aorta and then into the left ventricle utilizing constant pressure monitoring. The zero-pressure baseline was obtained by placing the pressure sensor in 37°C saline before measurements. After initial recordings were obtained, the catheter was exteriorized to the midcervical region, and the animals were allowed to recover from anesthesia and operation for at least 4 h before hemodynamic measurements were obtained.

Stressed left ventricular performance. After completion of baseline hemodynamic measurements, the animals were anesthetized with thiobutabarbital (Andrew Lockwood Associates). Approximately 40 min was allowed for complete anesthesia before measurements of stressed left ventricular pumping capacity were obtained. The left femoral artery was then exposed, and a 0.64-mm thermistor microprobe (Columbus Instruments) was advanced to the descending aorta. The contralateral femoral artery and the superior vena cava were canulated with PE-50 tubing for measurement of mean arterial pressure in the descending aorta and right atrial pressure. Thermodilution cardiac output and heart rate were measured simultaneously for calculation of stroke volume. To measure stressed left ventricular pressure development, the rat was intubated with a 20-gauge Angiocath catheter and ventilated with a volume-cycled respirator (Harvard Apparatus). A median sternotomy was then performed, and a 2-0 silk tie was positioned around the aorta. A 2- to 3-cm piece of polyethylene tubing (1.75 mm inside diameter) was placed over the tie and used as an occlusion device. The aorta was occluded for 2 to 3 s to produce isovolumetric (except for coronary flow) contractions. The peak left ventricular pressure developed was determined by measuring the difference in peak systolic and end-diastolic pressures after 5 stable beats.

Isolated left ventricular pressure–volume relation. After completion of all measurements, potassium chloride was injected rapidly into the right atrial catheter to arrest the heart in diastole. Pressure–volume data were recorded using methods described earlier (7,17,19). Briefly, the heart was rapidly removed, and the right ventricle was incised. A double-lumen catheter attached to a pressure transducer (Statham 231d, Gould) and an infusion pump (Sage 341, Orion Research) were passed into the left ventricle and secured with an aortic ligature. The atrioventricular groove was identified, and a ligature was passed around the heart and tied to isolate the left atrium from the left ventricle. After gentle aspiration of the left ventricular cavity to remove any residual blood and to reduce the pressure to −5 mm Hg, normal saline was infused at 1 ml/min into the suspended left ventricle while pressure was recorded. Saline was infused until the pressure increased to 40 mm Hg, and volume was determined from the infusion rate. Three curves were obtained from each ventricle within 10 min of the cardiac arrest, and the averaged values of volume at given pressures were reported.

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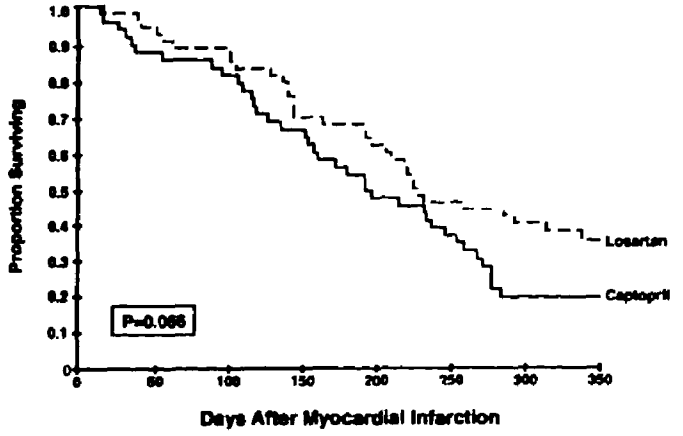

Figure 1. Kaplan-Meier curves in rats with a moderate to large infarction treated with captopril and losartan (2 g/liter drinking water each). One-year median survival in captopril-treated rats was 201.5 days versus 236.0 days losartan-treated rats (log rank p = 0.066).

Calculations. The time constant of left ventricular relaxation (tau) and chamber stiffness were fit to the following equations using published techniques (19):

$$dP/dt = -a(P - P_B),$$

where P_B is the intercept of pressure at $t = 0$; a is calculated by the least-squares method ($r > 0.99$), and tau $= -1/a$.

$$P = P_0 \exp(K_c V) \text{ (for } 3 \leq P \leq 40 \text{ mm Hg)},$$

where K_c, or chamber stiffness, is the slope of the relation $\ln P = K_c V + \ln P_0$.

Left ventricular cavity volume/wall volume. Ventricular cavity volume at a distending pressure of 10 mm Hg was determined from the passive pressure-volume relation. Left ventricular wall volume, V_w, was determined from the mass of the left ventricle (LV), such that V_w = LV mass (g)/1.06, where 1.06 is equal to muscle density. This relation assumes that ventricular muscle is incompressible.

Statistical analysis. The Student *t* test was used to test for differences in all hemodynamic and remodeling measurements as well as weight and age at time of myocardial infarction between the two treatment groups. Because not all rats were observed until natural death, survival analysis was used to adjust for these censored observations. The survival curve for each treatment was determined using the Kaplan-Meier method. Comparisons of the survival distributions between losartan- and captopril-treated rats were performed by a log-rank test (20). In planning the study, sample size calculations were performed with the intent to detect a 20% difference (i.e., 40% vs. 20% for 1-year survival) between treatments with a two-sided significance level of 0.05 and 80% power. Because possible differences in rates of thoracic infections could contribute to an alteration in group survival, an additional log-rank analysis was done that censored data from animals with a thoracic infection score of grade 3. The decision to analyze the data censored for lung infections was made prospectively, before initiation of the study.

Results

A total of 237 animals were entered into the study; 119 were randomized to captopril treatment and 118 to losartan treatment. In the captopril treatment group, 41 rats died before the ECG was recorded, 1 rat died during the ECG anesthetic period, and 31 rats had a small (<10%) infarction by ECG criteria. In the losartan treatment group, 45 rats died before the ECG was recorded, 1 died immediately after the ECG, and 21 had a small infarction by ECG criteria. All rats that died before the ECG was recorded died within 48 h after coronary ligation. Rats with ECG evidence of a small myocardial infarction were excluded from further analysis. Of the rats with ECG evidence of a small infarction, only one had a scar detectable at autopsy examination. In contrast, no rat with ECG evidence of moderate to large myocardial infarction had a grossly normal left ventricle.

Thus, 46 rats with a moderate or large myocardial infarction were treated with captopril, and 51 rats with a moderate to large myocardial infarction were treated with losartan. There were no significant differences in body weight (p = 0.684) or age at the time of myocardial infarction (p = 0.229). Infarct size in rats treated with captopril that died during the trial was 37 ± 4% (mean ± SD) (range 18% to 49%) versus 38 ± 4% (range 19% to 56%) in rats treated with losartan. In both treatment groups, there was one rat with an infarct size <20% and one rat with an infarct size >50%.

Survival data. The survival curves for rats with a moderate to large infarction that survived until the ECG are shown in Figure 1. Although there is no statistically significant difference in median survival between the two treatment groups—201.5 days for captopril versus 236.0 days for losartan (p = 0.066)—the survival curve for the losartan-treated rats is above that for the captopril treatment group starting within 2 weeks of coronary ligation. When the analysis included all rats that died within 48 h of the infarction, median survival in the captopril-treated group was 34.0 days versus 54.0 days for losartan treatment (p = 0.132).

Among rats with a moderate to large infarction that survived until the ECG was recorded, three rats in the losartan group had class 3 lung consolidation, a grading consistent with pneumonia (see Methods). There were no class 1 or class 2 lung consolidations in the losartan group. No rats in the captopril group had lung consolidation. In the losartan-treated rats with lung consolidation, the infarct sizes were 49%, 49% and 48%, respectively. These infarct sizes were in the upper 10% of infarct size for this study. Because lung consolidation was not evenly distributed between the two groups, data from these three animals were not censored for the primary analysis. Had these three rats been considered censored, the median survival for captopril-treated rats would be 201.5 days, versus 243.0 for losartan-treated rats ($p = 0.028$).

Hemodynamic variables and left ventricular remodeling. Hemodynamic and left ventricular remodeling measurements were obtained at 1 year in the surviving rats. When captopril- and losartan-treated rats were compared, there were no differences in left ventricular weights (1,073 ± 98 vs. 946 ± 213 mg), left ventricular systolic pressures (109 ± 19 vs. 99 ± 26 mm Hg), left ventricular end-diastolic pressure (14 ± 7 vs. 11 ± 9 mm Hg), dP/dt (5,271 ± 886 vs. 4,836 ± 1,276 mm Hg/s), cardiac index (315 ± 57 vs. 276 ± 58 ml/kg per min), time constant of relaxation (20.2 ± 3.4 vs. 19.4 ± 4.1 ms), stroke volume index (1.17 ± 0.20 vs. 0.97 ± 0.25 ml/kg per min), chamber stiffness constants (2.35 ± 0.71 vs. 2.20 ± 0.98), chamber volume/wall volume (0.79 ± 0.21 vs. 1.09 ± 0.40), ventricular length (17.5 ± 0.9 vs. 18.7 ± 1.5 mm), ventricular diameter (9.49 ± 0.78 vs. 10.01 ± 1.66 mm), wall thickness (2.22 ± 0.24 vs. 2.03 ± 0.21 mm) or myocardial infarction size (31 ± 4% vs. 38 ± 7%). The only differences were an increase in heart rate (293 ± 19 vs. 266 ± 15 beats/min, $p = 0.018$) and a decreased peak developed pressure (153 ± 21 vs. 180 ± 16 mm Hg, $p = 0.024$) in the losartan-treated rats.

Discussion

The present study confirms that mortality is increased in rats with heart failure after moderate to large myocardial infarction caused by coronary artery ligation. We also showed that there was no difference in survival with specific angiotensin II receptor blockade with losartan versus angiotensin-converting enzyme inhibition with captopril. Indexes of myocardial function and left ventricular geometry, obtained at 1 year in surviving rats, showed no differences between losartan- and captopril-treated rats. No differences were noted in heart weight, left ventricular pressures, dP/dt, cardiac index, time constant of relaxation or left ventricular volume and dimensions. There was an increase in heart rate and a decrease in peak developed pressure in infarcted rats treated with losartan. Although other studies have been performed to study the hemodynamic differences resulting from specific angiotensin II receptor blockade versus angiotensin-converting enzyme inhibition, to our knowledge this is the first to examine survival.

Need to use uncensored data. This study was designed with total mortality as the primary end point. We presented both the censored and the uncensored data because the analysis, in which animals with overt lung consolidation were censored, resulted in a significant increase in median survival in the losartan group. A total of three rats in the losartan group and none in the captopril group had lung consolidation. Because only three rats in the losartan group and no rats in the captopril group could potentially be censored on the basis of lung infection, censoring, which assumes a random occurrence between groups, could be interpreted as statistically inappropriate. The sample size in the present study and the incidence of infection were too small to determine whether the distribution of rats with infection in the losartan group was biologically significant. When lung consolidation was examined previously in rats with infarction, the incidence was not a function of infarct size (18), although in our study rats with lung consolidation had infarct sizes in the upper 10% of infarct sizes. Our interpretation of this observation is that lung consolidation, which is rare in healthy rats, occurs in rats after myocardial infarction, and the incidence may be increased in rats with larger infarctions.

Comparison with previous work. There are few published animal studies concerning survival after myocardial infarction. The present study design was based on the original captopril survival study by Pfeffer et al. (18), with the major difference that treatment was initiated on the day of the infarction; in the earlier study treatment was started on day 14. In both studies the dose of captopril was the same, 2 g/liter drinking water. In the study by Pfeffer et al., captopril improved survival in rats with moderate-sized infarctions, and there was no significant difference but a trend toward improved survival in rats with a large infarction. The median survival in the moderate and large infarct groups treated with captopril was 329 and 181 days, respectively. If the 14 days before the initiation of therapy is subtracted from the survival reported in our study, the median survival of 201.5 days for captopril-treated rats with a moderate to large infarction in our study is comparable. In our trial, after elimination of the rats that died before the ECG, 46 rats were treated with captopril and 51 with losartan compared with 35 rats with a moderate infarction and 37 with a large infarction assigned to captopril in the earlier study. Thus, despite the differences in study design and numbers, the survival data with captopril in both of these studies are similar.

In a second and more recent survival study of rats in heart failure treated with two doses of angiotensin-converting enzyme inhibition, the mortality rate at 1 year was 64.4% for rats with a moderate infarction and 100% for rats with a large infarction (21). Thus, it is clear that untreated rats with a moderate to large infarction have a very poor prognosis.

In the present study, there were no differences in any index of left ventricular remodeling, including data on ventricular geometry and wall thickness, in surviving rats treated with losartan or captopril. In addition, there were no differences in systolic function, diastolic function or infarct size among surviving rats. Although the present study was not designed specifically to examine remodeling, these data suggest that there were no differences in remodeling among the surviving

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rats treated with captopril or losartan after 1 year. A similar conclusion was reached when infarcted rats were treated for 6 weeks with enalapril or losartan and there were no differences in cardiac hypertrophy, minimal coronary vascular resistance or myocardial interstitial fibrosis (16).

Captopril and losartan may have divergent effects on kinin and prostaglandin metabolism (10,11). However, losartan has no bradykinin-potentiating effects, and it is unclear whether losartan affects the prostaglandin system (22–25). Although it has been postulated that the beneficial effects of angiotensin-converting enzyme inhibitors in the treatment of heart failure may be caused in part by elevation of bradykinin or prostaglandin levels, our data suggest that specific blockade of angiotensin II is primarily responsible for the survival benefits attributed to angiotensin-converting enzyme inhibitors in the rat model of heart failure.

Although this survival study compared angiotensin-converting enzyme inhibition with direct angiotensin II receptor blockade, earlier work from our laboratory showed that the hemodynamic effects of losartan and captopril in rats with heart failure after myocardial infarction were similar (15). Although the conclusions reached here apply only to the doses of agents used, the justification for testing these doses is that the captopril dose has been used in previous studies (7,18), and the losartan dose has similar hemodynamic effects, as noted before (15).

Timing of treatment. Although the original studies examining treatment with angiotensin-converting enzyme inhibitors after myocardial infarction were done after healing of the infarct, earlier treatment regimens are now being favored. When begun 14 days after experimental infarction, captopril has been shown (21) to affect ventricular remodeling favorably and to prolong survival in rats. Other work using the rat infarction model has confirmed that angiotensin-converting enzyme inhibition is comparable to losartan when started 2 to 3 weeks after myocardial infarction (25). Clinical trials also have shown a benefit when treatment is started 3 to 9 days after infarction (4), and data now show that initiating treatment within 24 h of an anterior wall infarction improves survival (26).

Study limitations. The lack of a placebo arm in the present trial has to be addressed. In designing the present study, our intention was to compare the effects of specific angiotensin II blockade with those of angiotensin II converting enzyme inhibition in rats with heart failure after a moderate to large infarction. Inclusive of operative mortality, ~35% of rats undergoing coronary ligation in our laboratory have moderate to large myocardial infarction. Operation was performed in 237 rats to obtain 97 animals for the present study. In planning the study, the sample size calculations were performed with the intent to detect a 20% difference between treatments with a two-sided significance level of 0.05. Had we chosen to include a placebo arm, to achieve that level of significance and power with three treatment arms would have required us to operate on 944 rats. Because the beneficial effects of angiotensin II converting enzyme inhibition are already well defined in both rats and people after myocardial infarction, we concluded that there was no compelling reason to warrant a placebo heart failure group.

When a study shows no difference between groups, the issue of statistical power must also be addressed. The study was designed to have a statistical power of 80%; thus, the possibility of a beta error, or a failure to detect a difference between two treatment groups, such as between losartan and captopril, when a difference actually exists is 20%. Thus, the power of the study was adequate to detect a difference between the two drugs with 80% confidence.

Although it is now established from clinical studies that survival after anterior wall myocardial infarction is improved with treatment with angiotensin-converting enzyme inhibitors initiated immediately after infarction (26), true first-day therapy is not feasible in our rat model of postinfarction heart failure. Even though losartan or captopril was available in the rat's drinking water, we observed that for the first 1 to 2 days after coronary artery ligation, rats do not eat or drink. For protocol considerations, therefore, our primary survival analysis was for those rats that lived >48 h after coronary artery ligation.

Our study showed no differences in any indexes of left ventricular remodeling among the surviving rats at 1 year, but to conclude that no differences existed may be misleading. Because so few rats survived to undergo hemodynamic and remodeling studies, we lacked statistical power to exclude a difference in remodeling. However, the major purpose of our study was to examine survival rather than remodeling.

Conclusions. In the present model, there was no difference in survival between captopril and losartan. Because the original captopril survival study in rats (18) accurately predicted the beneficial outcome of the clinical studies, it is reasonable to use the present data as the rationale for a clinical survival trial of angiotensin-converting enzyme inhibition versus direct angiotensin II receptor blockade.

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References

1. The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure: results of the cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med 1987;316:1429–35.
2. Cohn JN, Johnson G, Ziesche S, et al. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. N Engl J Med 1991;325:303–10.
3. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 1991;325:293–302.
4. Pfeffer MA, Braunwald E, Moye E, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction—results of the Survival and Ventricular Enlargement Trial. N Engl J Med 1992;327:669–77.
5. The AIRE Investigators. The Acute Infarction Ramipril Efficacy (AIRE) Study. Lancet 1993;52:821–8.
6. Lindpaintner K, Ganten D. The cardiac renin-angiotensin system An

appraisal of present experimental and clinical evidence. Circ Res 1991;68:905–21.

7. Raya TE, Gay RG, Aguirre M, Goldman S. Importance of vasodilation in prevention of left ventricular dilation after chronic large myocardial infarction in rats: a comparison of captopril and hydralazine. Circ Res 1989;64:330–7.
8. Cohn JN, Archibald DG, Ziesche S, et al. Effect of vasodilator therapy on mortality in chronic congestive heart failure: results of a Veterans Administration Cooperative Study. N Engl J Med 1986;314:1547–52.
9. Hirsch AT, Talsness CE, Schunkert H, Martin P, Dzau VJ. Tissue-specific activation of cardiac angiotensin converting enzyme in experimental heart failure. Circ Res 1991;69:475–82.
10. Linz W, Scholkens BA. Role of bradykinin in the cardiac effects of angiotensin converting enzyme inhibitors. J Cardiovasc Pharmacol 1992;20 Suppl 9:S83–90.
11. Schror K. Role of prostaglandins in the cardiovascular effects of bradykinin and angiotensin-converting enzyme inhibitors heart failure. J Cardiovasc Pharmacol 1992;20 Suppl 9:68–73.
12. Mimran A, Targhetta R, Laroche B. The antihypertensive effect of ceronapril. Evidence for an influence of the kinins. Hypertension 1988;2:73–7.
13. Re RN. The cellular biology of angiotensin: paracrine, autocrine and intracrine actions in cardiovascular tissues. J Mol Cell Cardiol 1989;21 Suppl V:63–69.
14. Farhy RD, Ho KL, Carretero OA, Scicli AG. Kinins mediate the antiproliferative effect of ramipril in rat carotid artery. Biochem Biophys Res Commun 1992;182:283–8.
15. Raya TE, Fonken SJ, Lee RW, et al. Hemodynamic effects of direct angiotensin II blockade compared to converting enzyme inhibition in rat model of heart failure. Am J Hypertens 1991;4:334s–40s.
16. Schieffer B, Wirger A, Meybrunn M, et al. Comparative effects of chronic angiotensin-converting enzyme inhibition and agiotensin II type receptor blockade on cardiac remodleing after myocardial infarction in the rat. Circulation 1994;89:2273–82.
17. Raya TE, Gay GG, Lancaster L, Aguirre M, Moffett BA, Goldman S. Serial changes in left ventricular relaxation and chamber stiffness after large myocardial infarction in rats. Circulation 1988;77:1424–31.
18. Pfeffer MA, Pfeffer JM, Steinberg C, Finn P. Survival after an experimental myocardial infarction: beneficial effects of long-term therapy with captopril. Circulation 1985;72:406–12.
19. Pennock GD, Raya TE, Bahl JJ, Goldman S, Morkin E. Combination treatment with captopril and the thyroid hormone analogue 3,5-diiodothyropropionic acid: a new approach to improving left ventricular function in heart failure. Circulation 1993;88:1269–98.
20. Rosner B. Fundamentals of Biostatistics 4th ed. Belmont, CA: Wadsworth 1995.
21. Wollert KC, Studer R, von Bulow B, Drexler H. Survival after myocardial infarction in the rat: role of the angiotensin-converting enzyme inhibition. Circulation 1994;90:2457–67.
22. Wong PC, Chiu AT, Price WA, et al. Non peptide angiotensin receptor antagonists. I. Pharmacological characterization of 2-n-butyl-4-chloro-1-(2-chlorobenzyl)imidazole-5-acetic acid, sodium salt (S-8307). J Pharmacol Exp Ther 1988;247:1–7.
23. Chiu AT, McCall DE, Price WA, et al. Non peptide angiotensin II receptor antagonists. VII. Cellular and biochemical pharmacology of DuP 753, an orally active antihypertensive agent. J Pharmacol Exp Ther 1990;252:711–32.
24. Martorana PA, Kettenbach B, Brelpohl G, Linz W, Scholkens BA. Reduction of infarct size by local angiotensin converting enzyme inhibition is abolished by a bradykinin antagonist. Eur J Pharmacol 1990;182:395–6.
25. Smits JF, Krimpen CV, Shoemaker RG, Cleutjens JP, Daemen MJ. AT-II receptor blockade after myocardial infarction in rats: effects on hemodynamics, myocardial DNA synthesis, and interstitial collagen content. J Cardiovasc Pharmacol 1992;20:772–8.
26. Ambrosioni E, Borghi C, Magnani B, and SMILE Investigators. The effect of the angiotensin-converting enzyme inhibitor zofenopril on mortality and morbidity after anterior myocardial infarction. N Engl J Med 1995;332:80–5.